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UNILATERAL INTRACEREBRAL MORPHINE INJECTIONS: BILATERAL BIOELEC--ETC(U)
JUL 76 H TEITELBAUM, J C BLOSSER

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The anterior amygdala region of the brain was subjected to daily unilateral injections of either 2.7 or 9.0 µg of morphine sulfate. Initial administration produced epileptiform patterns at the injection site and at the homotopic site in the contralateral hemisphere. While tolerance developed at the initial injection site after repeated administration, the contralateral site retained normal sensitivity

micrograms

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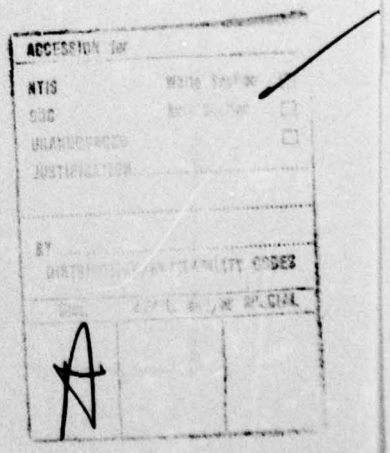
20. ABSTRACT (continued)

to the drug. As an example of cellular adaptation to chemical stress, the study of opiate tolerance provides a useful toxicological model for radiation reasearch.

SUMMARY
(Nontechnical)

Drug tolerance is seen after repeated treatment with opiates, barbiturates and alcohol. The mechanism for this altered sensitivity to drugs is poorly understood. One theory is that the blood-brain barrier is altered so that less drug gets into the brain in tolerant organisms.

The present experiment demonstrates that tolerance to morphine can be developed in a discrete brain region where the drug is directly injected into this region, bypassing the blood-brain barrier.



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INTRODUCTION

Drug tolerance is a condition which is characterized by a loss of sensitivity to the pharmacological properties of a drug as a result of repeated exposure. Because it can be produced by both intravenous and intracerebral injections of opiates or barbiturates,[3,5] functional alteration of neural cells most probably contributes to the development of tolerance to these drugs. Identifying mechanisms underlying the development of tolerance to morphine in the CNS is complicated by secondary drug-induced changes in bioelectric and metabolic activity which may not contribute to the development of the tolerant state. One possible approach to this problem is to make use of a mirror-focus preparation and compare the drug treated region in one hemisphere with its morphological homologue in the contralateral hemisphere.

Morrell[4] has taken advantage of commissural projections between homologous regions of the two cerebral hemispheres to induce bilateral epilepsy following unilateral treatment with a suitable irritant that causes the epileptic discharge pattern to be propagated to its mirror focus in the opposite hemisphere. Since the mirror-focus cells have never come in direct contact with the epileptogenic agents, any alteration in their metabolism is due solely to epilepsy. The amygdala is one such region in which seizures generated by electrical stimulation of one amygdala propagate by commissural projections to the contralateral amygdala.[1,4] Since the anterior amygdala of the rat has been reported to have a high concentration of opiate receptors,[2] it appears well suited for studies of morphine tolerance by intracerebral injections. The initial questions were: (1) what response would be obtained if morphine sulfate was injected directly into this subcortical region; (2) would there be an effect in the homotopic region of the opposite hemisphere; and (3) could tolerance be lateralized at the injection site?

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METHODS

Fifteen male Tac:N(SD) fBR rats anesthetized with sodium pentobarbital were implanted with bilateral cannula-recording electrode assemblies in the anterior amygdaloid region of the brain. The permanently implanted cannula serves as a guide for a smaller fluid delivery cannula and as one pole of the bipolar recording assembly that monitors bioelectric activity changes at the injection site. Opiate solutions or saline, the control solution, were delivered at a rate of 0.03 μl per second over a 30-second period.

RESULTS AND DISCUSSION

After injecting morphine sulfate (2.7 or 9.0 μg) unilaterally into the anterior amygdala, a spike and wave pattern was observed at the injection site in 10 of 15 animals (Figure 1, top and middle left). The spike and wave pattern at the contralateral amygdala occurred 15-30 minutes postinjection and persisted for 3-4 hours (Figure 1, lower left) each day. Saline produces no effect at either recording site. After repeated daily administration of opiates, tolerance, manifested by a diminished bioelectric response, developed at the injection site (Figure 1, top right).

Despite the daily appearance of sustained epileptiform patterns at the mirror focus in the opposite hemisphere, there is no transfer of tolerance to the opposite hemisphere. When a similar dose of morphine is administered directly to the previously untreated amygdala, normal sensitivity to the drug is seen at the mirror focus (Figure 1, middle right). Furthermore, kindled spike and wave patterns are seen at the original injection site (Figure 1, lower right). Levorphanol (3.0 μg) causes a similar response when injected into the amygdala. In addition, cross tolerance between the two opiates has been observed. However, dextrorphan (10.8 μg) elicits no bioelectrical response (Figure 2).

The bioelectric response elicited by morphine and the eventual appearance of tolerance is not a toxic or nonspecific effect because (1) EEG recordings always return to the original base-line levels following drug administration;

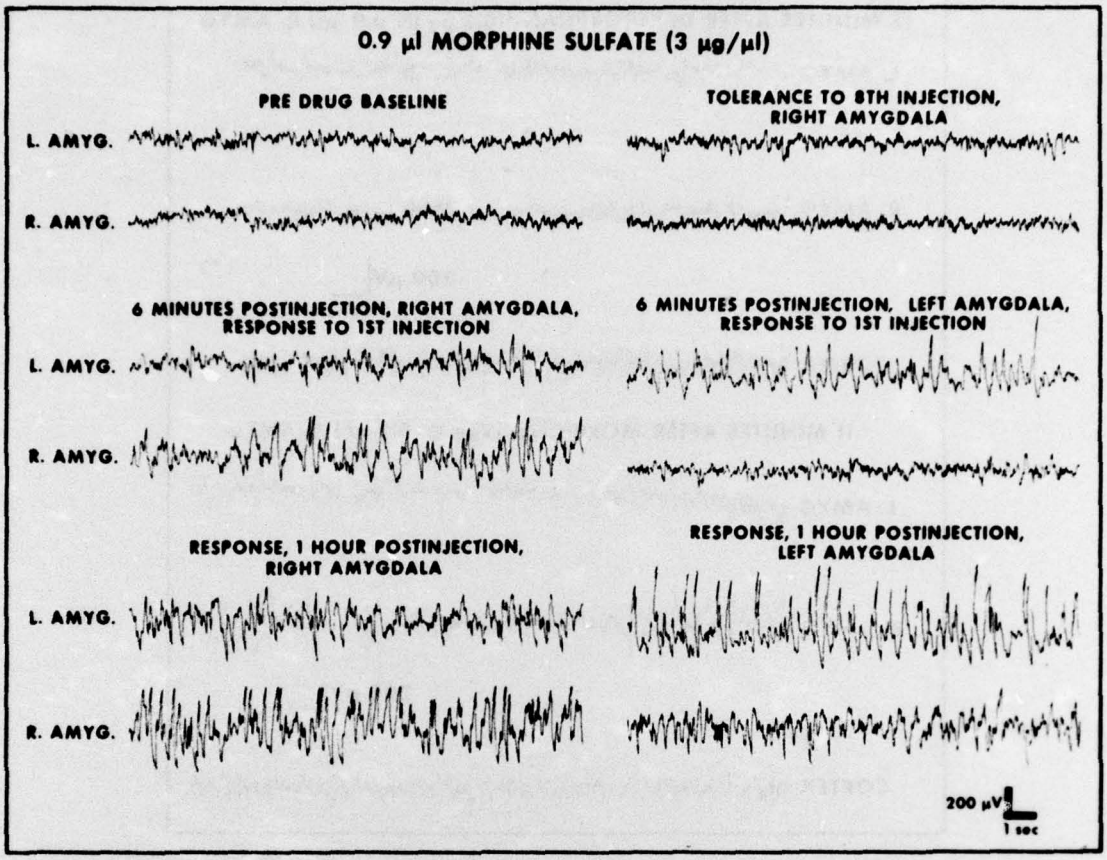

Figure 1. Effect of 2.7 µg morphine sulfate injected i.c. on the bioelectric activity of the anterior amygdaloid region (Rat 344)

(2) evoked potentials (produced by electrical stimulation of the contralateral amygdala) recorded from the opiate treated amygdala are normal, suggesting that there is no acute damage to responsive neurons; (3) tolerance can be overcome by administration of a morphine dose four times that of the original dose; (4) the response to the opiates is stereospecific; levorphanol but not dextrorphan mimics the action of morphine; and (5) the location of the cannula is critical. Histological examination of the cannula positions of successful and unsuccessful cases revealed that those cannulas placed bilaterally over the anterior amygdaloid region gave bilateral opiate responses. If the cannula tips were located in

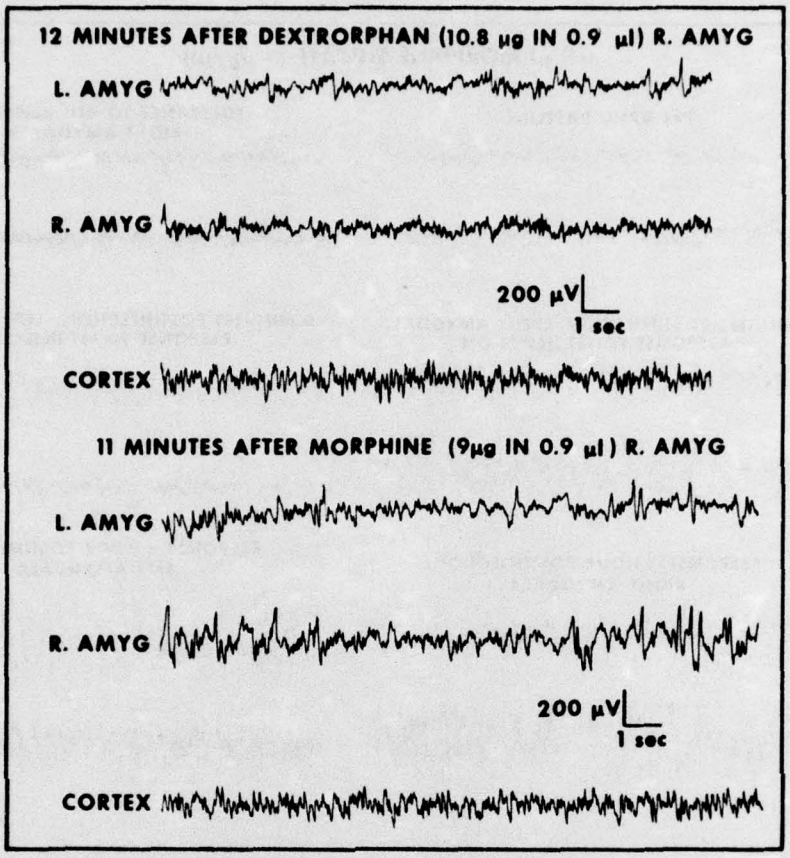

Figure 2. Comparison of the effects of dextrorphan and morphine injected into the right amygdala. Morphine was administered 2 days after dextrorphan. Spike and wave patterns are most evident at the injection site of morphine. Cortical readings remain unaltered. (Rat 408)

the lateral striatum, or deep in the pyriform cortex, no morphine response was obtained. The localization of this bioelectric response to the anterior amygdala is consistent with reports of high concentrations of opiate receptors in this subcortical region. In addition, preliminary studies indicate that preinjection of naloxone (0.9 µg), a specific narcotic antagonist, blocks the response to morphine (0.9 µg).

These findings show that unilateral tolerance can be produced with unilateral intracerebral microinjections of morphine sulfate into the amygdala.

Further, the morphine-induced epileptiform patterns shared by both amygdala do not contribute to the development of drug tolerance.

While tolerance has been previously demonstrated with the direct intracerebral administration of opiates and barbiturates,[3,5] this is the first time lateralization of opiate tolerance has been demonstrated. This unilateral alteration in drug sensitivity may be related to an ipsilateral alteration in biochemical activity not seen at the contralateral site of the brain.

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